

COMMENTS AND RESPONSES

Implications of the Multicenter Automatic Defibrillator Implantation Trial-II

TO THE EDITOR: Dr. Al-Khatib and colleagues (1) are to be commended for their evaluation of the cost-effectiveness of implantable cardioverter defibrillators (ICDs) in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. At 20 months, mortality was 14.2% in the ICD group and 19.8% in the controls, an absolute difference of 5.6 percentage points (2). The cost of treatment in the ICD group was estimated at \$131 490 compared with \$40 661 in the medical therapy group—a difference of \$90 829 for a gain in life-years of 1.8 years (1). The authors found ICDs to be marginally cost-effective, with a base-case estimate of the incremental cost-effectiveness ratio of \$50 500 per life-year gained. Sensitivity analysis suggested that the ratio could vary greatly depending on the assumptions made. The ratio was especially sensitive to the effectiveness of the ICD.

The MADIT-II population comprised patients who had a previous myocardial infarction (MI) and whose left ventricular ejection fraction was 0.3 or less (2). Patients with a history of MI have been shown to benefit from β -blockade and angiotensin-converting enzyme inhibition. More recently, aldosterone blockade has been shown to be both efficacious and cost-effective (3, 4). In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), patients with ejection fractions of 0.4 or less and evidence of heart failure were randomly assigned to receive eplerenone or placebo 3 to 14 days after MI. After a mean duration of 16 months, the absolute difference in survival was 2.3% (3). If one uses the Worcester Heart Attack database to project survival, the gain with eplerenone was 0.1337 year. The added cost was \$1391, which translates to an incremental cost-effectiveness ratio of \$10 402 per life-year gained (4).

It has been shown that ICDs do not reduce overall mortality within the first month after acute MI (5), and they do not favorably affect any mortality rate other than that associated with arrhythmic death (sudden cardiac death). Eplerenone reduces both all-cause mortality and sudden cardiac death, doing so almost immediately after MI (3, 6).

Differences in the populations and methods of these 2 studies make a direct comparison difficult; however, it is clear that pharmacotherapy is often more cost-effective than implantable devices or surgical interventions (7). There is tremendous concern over the cost of pharmacotherapy (8), which may be related to the fact that pharmaceuticals have not been traditionally covered by Medicare. Recent legislation will change that concern in large measure. However, when pharmacotherapy is life-saving and cost-effective, society should be encouraged to make such therapy available to all who need it.

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References

1. Al-Khatib SM, Anstrom KJ, Eisenstein EL, Peterson ED, Jollis JG, Mark DB, et al. Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann Intern Med.* 2005;142:593-600. [PMID: 15838065]
2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877-83. [PMID: 11907286]
3. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-21. [PMID: 12668699]
4. Weintraub WS, Zhang Z, Mahoney EM, Kolm P, Spertus JA, Caro J, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. *Circulation.* 2005;111:1106-13. [PMID: 15723981]
5. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* 2004;351:2481-8. [PMID: 15590950]
6. Pitt B, White H, Nicolau J, Martinez F, Gheorghide M, Aschermann M, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol.* 2005;46:425-31. [PMID: 16053953]
7. Winkelmayer WC, Cohen DJ, Berger ML, Neumann PJ. Comparing cost-utility analyses in cardiovascular medicine. In: Weintraub WS, ed. *Cardiovascular Health Care Economics.* Totowa, NJ: Humana Pr; 2003:329-56.
8. Weintraub WS, Shine K. Is a paradigm shift in US healthcare reimbursement inevitable? *Circulation.* 2004;109:1448-55. [PMID: 15051648]

TO THE EDITOR: Al-Khatib and colleagues (1) failed to emphasize a major limitation of their study: lack of applicability to persons living in developing countries—over one third of the world's population. Implantable defibrillators are too prohibitively expensive for these nations to even consider. Given that the major contribution to the global burden of cardiovascular disease is anticipated to arise from developing nations (2), it is an unfortunate reality that many deaths that could be prevented by ICDs will occur in these countries.

There is an urgent need for cheaper (even if significantly less sophisticated) devices to be marketed to developing nations. Life cannot be regarded as “expendable” in any country.

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References

1. Al-Khatib SM, Anstrom KJ, Eisenstein EL, Peterson ED, Jollis JG, Mark DB, et al. Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann Intern Med.* 2005;142:593-600. [PMID: 15838065]
2. Yusuf S, Vaz M, Pais P. Tackling the challenge of cardiovascular disease burden in developing countries [Editorial]. *Am Heart J.* 2004;148:1-4. [PMID: 15215784]

IN RESPONSE: Dr. Weintraub argues that eplerenone, an aldosterone blocker, is more cost-effective than the ICD. Although his estimated incremental cost-effectiveness ratio of \$10 402 per life-year gained for eplerenone seems much more favorable than our base-case ratio of \$50 500 per life-year gained for an ICD, we caution against these comparisons when the interventions are not compared head-to-head. Both MADIT-II and EPHESUS enrolled appreciably different patients. Whereas all patients in EPHESUS had clinical or radiographic

evidence of heart failure, half of the patients in MADIT-II did not. All patients in EPHEsus were enrolled 3 to 14 days after MI, but 88% of patients in MADIT-II had had an MI more than 6 months before enrollment. These differences make comparisons between eplerenone and ICD therapy difficult (1, 2).

Another reason to caution against such comparisons is that calculation of the incremental cost-effectiveness ratio depends on many assumptions. Unless these assumptions are identical, ratio comparisons are not valid. Among many other assumptions, the time horizon, the change of hazard over time, costs of both interventions, and intensity of follow-up visits are important. It is not clear to us what assumptions were used in the cost-effectiveness ratio calculated by Dr. Weintraub. On the basis of results of the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), Dr. Weintraub states that ICDs do not reduce mortality within the first month after MI. Although we agree with Dr. Weintraub's interpretation, we believe this question cannot be settled with 1 clinical trial—particularly because patients in the control group underwent coronary revascularization much more frequently than those in the ICD group during the course of DINAMIT (3). A recent analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) showed the risk for sudden death to be highest in the first 30 days after MI in patients with left ventricular dysfunction, heart failure, or both (4). Therefore, the question of whether an ICD is beneficial shortly after an MI deserves further examination.

Notwithstanding the ambiguities in Dr. Weintraub's letter, we agree with him on the following point: When pharmacotherapy is life-saving and cost-effective, society should be encouraged to make such therapy available to those who need it. Dr. Jafary brings up a good point regarding the limited access to ICDs in developing countries and the need for cheaper devices; however, affordability is a separate issue from cost-effectiveness. It is up to each country to decide how much of its wealth to invest in health care.

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References

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877-83. [PMID: 11907286]
2. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-21. [PMID: 12668699]
3. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* 2004;351:2481-8. [PMID: 15590950]
4. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med.* 2005;352:2581-8. [PMID: 15972864]

Managing People at High Risk for Diabetes

TO THE EDITOR: We are writing in response to the report by Eddy and colleagues (1). We have several questions about their simulations, conclusions, and representation of our work. Unlike the authors, we found a favorable cost-effectiveness ratio for the Diabetes Prevention Program lifestyle intervention (2).

The Archimedes model may or may not represent a quantum leap in diabetes modeling. For simulation models to aid decision making, they must be transparent and have face validity. By using complex differential equations fitted to empirical data, the Archimedes model can simulate an infinite number of physiologic processes. Unfortunately, the equations governing disease progression are not transparent. In contrast, Markov models can simulate only a finite number of health states. Yet, as demonstrated in the appendix to the report by Eddy and colleagues, Markov models are transparent and invite critics to debate their validity.

In this simulation, unlike previous simulations, the authors constrain the progression of hyperglycemia to reflect the increase in average fasting plasma glucose levels over the first 4 years of the Diabetes Prevention Program (approximately 0.11 mmol/L [2 mg/dL] per year) and over the first 14 years of the United Kingdom Prospective Diabetes Study (UKPDS) (approximately 0.17 mmol/L [3 mg/dL] per year). Therefore, to progress from fasting plasma glucose level of 5.93 mmol/L (107 mg/dL) at the start of the Diabetes Prevention Program to 11.16 mmol/L (201 mg/dL) at the time of evaluation for the UKPDS would take more than 30 years. Studies have clearly demonstrated that progression from normal to impaired glucose tolerance and ultimately to type 2 diabetes is not a linear process (3, 4). Instead, a threshold is reached followed by rapid decompensation and progression (5). In this simulation, the glycemic exposure associated with diabetes is also limited. In each of Eddy and colleagues' simulation strategies, "persons [with diabetes] whose HbA_{1c} [hemoglobin A_{1c}] level exceeded 7% were entered into an intensive diabetes treatment protocol designed to reduce their HbA_{1c} level to below 7% . . . [which] reduced HbA_{1c} levels to an average of 6.6%." In the U.S. population with self-reported diabetes, the median HbA_{1c} level is 7.5%; 41% of these individuals have HbA_{1c} levels greater than 8.0% (6).

The use of these data with the Archimedes model may explain why the progression of hyperglycemia appears inordinately slow and why diabetes appears to develop without important clinical sequelae. In the Diabetes Prevention Program Outcomes Study, 13% of participants progressing to diabetes had evidence of diabetic retinopathy on retinal photographs taken on average 3.1 years after diagnosis (7). Furthermore, we know that cardiovascular disease is common in diabetes, survival is decreased, and more than 50% of patients die of cardiovascular causes. How then, after 30 years of follow-up, with an average patient age of 81 years and after 72% of the cohort had developed diabetes, can Archimedes predict a 3% cumulative incidence of retinopathy, a 12% cumulative incidence of myocardial infarction, and 87% survival? We believe that this finding can be explained by the fact that hyperglycemia and diabetes were constrained not to progress. If hyperglycemia and diabetes do not progress, the risk for complications will be low and the benefits of delaying or preventing diabetes will be small. This theory also explains why prevention is not cost-effective. If late and expensive

complications do not develop in diabetic patients, then no intervention to prevent diabetes can improve health outcomes or provide economic value.

Finally, we take exception to the authors' misrepresentation of our model and the characterization of our model as "not validated." Our model has been extensively validated and referenced in published reports since 2002. Admittedly, it has been adapted and refined over time, but that is true of most models—including Archimedes. Indeed, because the Archimedes model was updated since the publication of initial validation studies and because the model was not previously used to model prediabetes, one could argue that Archimedes itself was "not validated."

If we were to believe the results of the authors' simulations, we would conclude that diabetes is not the clinical and public health problem that we know it to be. Projections derived from the Archimedes model simply do not reflect physiology or clinical reality. Because too few complications are predicted, diabetes prevention adds little value. Our model is transparent and has face validity. We stand by our results, and we believe that our conclusions are valid and that health policy should promote diabetes prevention in high-risk individuals (2).

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References

1. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med.* 2005;143:

251-64. [PMID: 16103469]

2. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005;142:323-32. [PMID: 15738451]

3. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol.* 1981;113:144-56. [PMID: 7468572]

4. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP. Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. *Diabetes.* 2004;53:160-5. [PMID: 14693710]

5. Ward WK, Beard JC, Halter JB, Pfeifer MA, Porte D Jr. Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus. *Diabetes Care.* 1984;7:491-502. [PMID: 6094129]

6. Saaddine JB, Engelgau MM, Beckles GL, Gregg EW, Thompson TJ, Narayan KM. A diabetes report card for the United States: quality of care in the 1990s. *Ann Intern Med.* 2002;136:565-74. [PMID: 11955024]

7. Hamman RF. Retinopathy in recent-onset diabetes and persons at high risk of diabetes in the Diabetes Prevention Program: late-breaking clinical trials [Abstract]. San Diego: 65th Annual Meeting of the American Diabetes Association; 2005.

IN RESPONSE: We are pleased to address the issues raised by Dr. Herman and his colleagues. Concerning glycemic progression, they are correct that we used UKPDS data to help build our model. We see that as a strength, not a weakness. The resulting model accurately simulates the progression of diabetes across the entire time horizon of our analysis—from impaired fasting glucose and impaired glucose tolerance (it independently predicted the rates in the Diabetes Prevention Program) through to clinical diabetes and for at least 15 years thereafter.

Dr. Herman and associates argue for a faster rate of glycemic progression. They assume that everyone progresses from "diabetes onset" to "clinical diabetes" in exactly 10 years (1), which implies a rate that is greater than twice that seen in the UKPDS. We see several problems with this assumption, beyond the fact that it contradicts the UKPDS. They based their assumption on 2 papers (2, 3) that estimated that retinopathy first begins to appear in populations about 4 to 7 years before clinical diagnosis. These papers, in turn, cited a study that followed 30 people after onset of diabetes and noted that the first case of retinopathy appeared 5 years after onset (4). The 10-year assumption comes from adding 5 years (from onset to retinopathy) and 4 to 7 years (from retinopathy to clinical diagnosis). First, 5 years was the shortest time from diabetes onset to retinopathy. The study actually showed a wide variation, and retinopathy developed in only 8 of the 30 (27%) patients after a minimum of 10 years of follow-up. Second, 4 to 7 years is the time of the first case in a sample. The authors appear to have mistakenly interpreted these values to mean that retinopathy appears 4 to 7 years before clinical diabetes in everyone. In fact, the time of occurrence of retinopathy varied widely and was 10 to 20 years after clinical diagnosis on average. These papers actually contradict a fixed 10-year transit time.

Dr. Herman and colleagues point to the frequency of early retinopathy in people in the Diabetes Prevention Program after onset of diabetes (13% within 3 years) and suggest that the complications we calculated are too low. The rates we reported were for advanced retinopathy in people who did not have diabetes at the start of the calculation. We calculated that 8% of people with prediabetes developed early retinopathy within 3 years, which fits with the estimate of

13% in people who have diabetes. We also note that our model matches quite closely the progression of retinopathy seen in the UKPDS and other trials (5).

Concerning myocardial infarctions, the 12% and 50% values are measuring entirely different things and are not comparable. To evaluate the accuracy of our model for calculating cardiovascular events, we recommend looking at the rate actually seen in the Diabetes Prevention Program after 3 years, 7.3 events per 1000 person-years (6). We calculated 8.4 events per 1000 person-years. About 40% of people with diabetes die of ischemic heart disease (7). For the population from the Diabetes Prevention Program, we calculated 28%, which is right on target given the differences in populations and time horizons. Additional validations of myocardial infarction rates in 12 clinical trials, including UKPDS and a prospective prediction of CARDS (Collaborative Atorvastatin Diabetes Study) are described elsewhere (1, 5).

We can correct other misunderstandings. First, we did not assume that glycemic progression is a “linear process”; in our model, progression varies from person to person and is not linear even for any particular person. Second, we did not “constrain” diabetes progression nor did we fix HbA_{1c} levels at 6.6%. The physicians in our simulation followed American Diabetes Association guidelines and treated people to achieve a target of 7% (making the average less than 7%). From that point on, we assumed the degree of control would gradually deteriorate as seen in the intensive care group of the UKPDS. Third, we used the same model that had been validated against 18 clinical trials (5); those validations *do* apply to this analysis. Fourth, we have validated the model for analyzing prediabetes; we did a blinded validation against the Diabetes Prevention Program itself (1, 5). Fifth, we have searched the literature again and still cannot find any validations of the model that Dr. Herman and his colleagues used. Specific references might help.

In addition to the issues that the authors raise in their letter, other aspects of their model may help explain why they achieved different results. Some examples from their paper and technical report (2) are as follows: HbA_{1c} levels increase at a constant annual rate of 0.2% during clinical diabetes (technical report, page 22; note that the rate was 0.11% in the UKPDS); at the beginning of clinical diabetes, no one yet has any signs of retinopathy (technical report, page 88); the annual probability that a person with prediabetes progresses to diabetes does not depend on how long they have had impaired fasting glucose or impaired glucose tolerance (paper, page 324); lifestyle reduces the probability of progressing from prediabetes to diabetes by a fixed 58% (paper, page 324; note that for patients in the Diabetes Prevention Program, the effect declined steadily over time and was about 44% after 4 years of follow-up); costs are multiplicative (paper, page 326); retinopathy and neuropathy do not affect costs (paper, page 326); blood pressure and levels of total serum cholesterol and high-density lipoprotein can only be categorized as “normal” or “above normal” (technical report, pages 39 and 43); risk for coronary heart disease in people with early (preclinical) diabetes is calculated from the UKPDS risk engine (paper, page 325), which was designed to be used after a patient develops clinical diabetes; and the annual risk for end-stage kidney disease does not depend on how long someone has had diabetes, clinical nephropathy, or blood pressure levels (technical report, page 12). These and other assumptions, some of which are summarized in the appendix to our paper, may deserve reconsideration.

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References

- Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005;142:323-32. [PMID: 15738451]
- Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care.* 1992;15:815-9. [PMID: 1516497]
- Thompson TJ, Engelgau MM, Hegazy M, Ali MA, Sous ES, Badran A, et al. The onset of NIDDM and its relationship to clinical diagnosis in Egyptian adults. *Diabet Med.* 1996;13:337-40. [PMID: 9162609]
- Jarrett RJ. Duration of non-insulin-dependent diabetes and development of retinopathy: analysis of possible risk factors. *Diabet Med.* 1986;3:261-3. [PMID: 2951182]
- Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. *Diabetes Care.* 2003;26:3102-10. [PMID: 14578246]
- Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care.* 2005;28:888-94. [PMID: 15793191]
- Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al., eds. *Diabetes in America*. 2nd ed. Washington, DC: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:233-58. NIH publication no. 95-1468. Available at <http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter11.pdf>.

CLINICAL OBSERVATIONS

Hepatotoxicity Associated with Supplements Containing Chinese Green Tea (*Camellia sinensis*)

TO THE EDITOR: *Background:* Recent reports have identified an association between hepatotoxicity and health supplements containing green tea extract (*Camellia sinensis*).

Objective: To present a new case study involving a patient who exhibited a positive response to a rechallenge and to summarize previous reports of *C. sinensis*-associated hepatotoxicity.

Methods and Findings: A 37-year-old Hispanic woman was evaluated for a 10-day history of diffuse abdominal pain, nausea, and jaundice. She had been using a weight-loss supplement called The Right Approach Complex (Pharmanex, Provo, Utah) for 4 months. She was afebrile. Her serum aspartate aminotransferase (AST) level was 1783 U/L (reference range, 17 to 39 U/L), her serum alanine aminotransferase (ALT) level was 1788 U/L (reference range, 8 to 39 U/L), her serum total bilirubin level was 200 μ mol/L (11.7 mg/dL) (reference range, 7 to 24 μ mol/L [0.4 to 1.4 mg/dL]), her serum

direct bilirubin level was 169 $\mu\text{mol/L}$ (9.9 mg/dL) (reference range, 0 to 3 $\mu\text{mol/L}$ [0 to 0.2 mg/dL]), her serum alkaline phosphatase level was 238 U/L (reference range, 39 to 113 U/L), and her serum albumin level was 650 $\mu\text{mol/L}$ (reference range, 580 to 800 $\mu\text{mol/L}$). Results of serologic tests for antibodies against hepatitis A IgM, hepatitis C, and hepatitis B surface antigen were negative. An anti-nuclear antibody titer was weakly positive (1:40, speckled); results of tests for antiliver–kidney microsomal, anti-dsDNA, anti-smooth muscle, and antimitochondrial antibodies were negative. Liver biopsy revealed marked interface necrosis and inflammation and mild lobular inflammation. Cholecystectomy and intraoperative cholangiography were performed; the gallbladder and bile ducts were normal, and there was no evidence of cholecystitis or stones. The patient was discharged on day 13. One month later, her serum AST level was 79 U/L, her serum ALT level was 92 U/L, and her serum total bilirubin level was 33 $\mu\text{mol/L}$ (1.9 mg/dL).

Approximately 1 year later, the patient was again admitted with a 1-week history of diffuse abdominal pain and jaundice. She reported loss of appetite, mild nausea, and pruritus. Approximately 1 month earlier, she had resumed taking The Right Approach Complex but stopped taking it 1 week before presentation because of dysphagia. On admission, her serum AST level was 977 U/L, her serum ALT level was 1131 U/L, her serum total bilirubin level was 200 $\mu\text{mol/L}$ (11.7 mg/dL), and her international normalized ratio was 1.3. Her serum acetaminophen level was less than 66 $\mu\text{mol/L}$ (reference range, 35 to 130 $\mu\text{mol/L}$). Results of repeated screens for infectious and autoimmune causes were negative. On day 8 of hospitalization, the patient's serum AST level was 816 U/L, her serum ALT level was 877 U/L, her serum total bilirubin level was 49 $\mu\text{mol/L}$ (2.9 mg/dL), and her serum alkaline phosphatase level was 165 U/L. The patient was discharged, and her physician stressed that she should not resume taking the weight-loss supplement or any others with similar ingredients. One month later, her serum AST and ALT levels were 80 and 69 U/L, respectively, and her serum total bilirubin level was 20.52 $\mu\text{mol/L}$ (1.2 mg/dL). Six months later, her serum AST level was 27 U/L, her serum ALT level was 25 U/L, her serum alkaline phosphatase level was 85 U/L, and her serum total bilirubin level was 17 $\mu\text{mol/L}$ (1.0 mg/dL).

Conclusion: The Table summarizes published studies that associate products containing *C. sinensis* with hepatotoxicity, usually with a mixed hepatocellular–cholestatic picture (1–5). Most patients were younger than 40 years of age and 7 of 9 were women, perhaps reflecting greater susceptibility or greater use of such supplements among women. All patients improved after stopping the products and had normal liver test results within 4 months after they stopped taking the supplement. Chronic, self-sustaining liver injury was not found. In view of the severity of injury, continuing or long-term use

in the setting of injury could lead to serious liver failure. Features to suggest an immunoallergic cause were absent in our case and in the other reports. The pathogenesis remains unknown.

It is difficult to establish a definitive causal relationship between extracts of *C. sinensis* and the reported cases of hepatotoxicity because of the multiplicity of ingredients and coingestants in many of the cases. In our patient, the temporal pattern of *C. sinensis* administration and liver enzyme abnormalities (with a positive rechallenge and exclusion of other possible causes) strongly suggested that the supplement was the inciting agent for both episodes of severe, symptomatic drug-induced liver injury. Extract of *C. sinensis* is the most probable cause of hepatotoxicity in this patient because 1) this extract is the major ingredient of the supplement by weight (383.3 mg per 3 capsules); 2) there are now several recent reports of similar symptomatic hepatotoxicity in patients using *C. sinensis* extracts; and 3) other ingredients of the supplement have not been reported to be hepatotoxic at levels found in 3 capsules (calcium, 167 mg; chromium, 67 μg ; magnolia extract, 100 mg; aqueous epimedium extract, 100 mg; β -sitosterol, 40 mg; banaba leaf extract, 11 mg; and vanadium, 10 μg). Although Chinese green tea is widely touted as a cytoprotective antioxidant and panacea, we believe that large amounts (5) or concentrated preparations of *C. sinensis* are dangerous and should be avoided.

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Potential Financial Conflicts of Interest: None disclosed.

References

1. Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut [Letter]. *Ann Intern Med*. 2005; 142:477-8. [PMID: 15767636]
2. Porcel JM, Bielsa S, Madronero AB. Hepatotoxicity associated with green tea extracts [electronic letter]. Accessed at www.annals.org on 3 June 2005.
3. Pedros C, Cereza G, Garcia N, Laporte JR. [Liver toxicity of *Camellia sinensis* dried etanolic extract] [Letter]. *Med Clin (Barc)*. 2003;121:598-9. [PMID: 14622530]
4. Garcia-Moran S, Saez-Royuela F, Gento E, Lopez Morante A, Arias L. [Acute hepatitis associated with *Camellia thea* and *Orthosiphon stamineus* ingestion] [Letter]. *Gastroenterol Hepatol*. 2004;27:559-60. [PMID: 15544745]
5. Thiolet C, Menecier D, Bredin C, Moulin O, Rimlinger H, Nizou C, et al. [Acute cytotoxicity induced by Chinese tea] [Letter]. *Gastroenterol Clin Biol*. 2002;26:939-40. [PMID: 12434106]
6. Vial T, Bernard G, Lewden B, Dumortier J, Descotes J. [Acute hepatitis due to Exolise, a *Camellia sinensis*-derived drug] [Letter]. *Gastroenterol Clin Biol*. 2003;27: 1166-7. [PMID: 14770123]

Table. Liver Injury Associated with Supplements Containing *Camellia sinensis**

Study, Year (Reference)	Age, y	Sex	Ethnicity	Substance Implicated	Approximate Duration of Exposure before Symptom Onset, d	Approximate Cumulative Dose of Extract Consumed, g†	Rechallenge Results	Peak Serum Alanine Aminotransferase Level, U/L	Peak Serum Alkaline Phosphatase Level, U/L
Bonkovsky, 2005‡	37	Female	Hispanic	The Right Approach (Pharmanex, Provo, Utah)	120	240	Positive	1788	238
Bonkovsky, 2005§	38	Female	Hispanic	The Right Approach (Pharmanex, Provo, Utah)	16	32	None	1166 (hospital day 2)	212
Stevens et al., 2005 (1)	27	Male	NR	Hydroxycut (MuscleTech, Mississauga, Ontario)	28	41	–	3962	171
Stevens et al., 2005 (1)	30	Male	NR	Hydroxycut (MuscleTech, Mississauga, Ontario)	5	5.9	–	45	530
Porcel et al., 2005 (2)	53	Female	NR	Fitofruit grasas acumuladas (Gerble, Barcelona, Spain)	16	27¶	–	1259	187
Pedros et al., 2003 (3)	35	Female	White	Exolise (Arkopharma, Carros, France)	35	26	–	1558	340
Pedros et al., 2003 (3)	29	Female	White	Exolise (Arkopharma, Carros, France)	45	68	–	1674	260
Garcia-Moran et al., 2004 (4)	25	Female	White	Camilina Akocapsulas (manufacturer not reported)	60	108	–	2398	164
Thiolet et al., 2002 (5)	39	Female	White	Oolong tea fine tonic (manufacturer not reported)	15	Not reported	Resumed supplement in 3 months; no increase in serum aminotransferase levels observed	45× normal	3× normal
Vial et al., 2003 (6)	46	Female	White	Exolise (Arkopharma, Carros, France)	75	Not reported	Serum alanine aminotransferase levels greater than 10× normal (rechallenge with Exolise and a second supplement)	>100× normal	2× normal

* Additional case reports not referenced in text are available from Porcel et al. NR = not reported.

† On the basis of history and dose size stated on package.

‡ One case reported; these findings were observed during first episode.

§ One case reported; these findings were observed during second episode.

|| Uncertain because of vague labeling.

¶ According to authors, each capsule contains 651 mg of green tea extract.

Table—Continued

Peak Serum Total Bilirubin Level, $\mu\text{mol/L}$ (mg/dL)	Peak Serum Direct Bilirubin Level, $\mu\text{mol/L}$ (mg/dL)	Peak Prothrombin Time, s	Imaging Results	Biopsy Results	Duration of Injury	Outcome
11.7	9.9	12.5	Ultrasonogram: coarsened echotexture suggestive of fatty infiltration	Marked periportal piecemeal necrosis; periportal inflammation; mild lobular inflammation; no plasma cells; negative trichrome stain	>1 month	Recovery; serum alanine aminotransferase level of 31 U/L on 4 November 2004
9.0	7.3	13.2	Ultrasonogram: normal postcholecystectomy findings	–	<2 months	Recovery; serum alanine aminotransferase level of 69 U/L on 27 January 2005
133 (7.8)	–	16	–	–	4 weeks	Recovery
133 (7.8)	–	15	Computed tomogram and endoscopic retrograde cholangiopancreatogram: normal	Cholestasis and portal inflammation	<2 months	Recovery
92 (5.36)	–	12.7	Ultrasonogram: hepatomegaly	–	<5 weeks	Recovery
323 (18.9)	222 (13)	–	Ultrasonogram: normal	–	–	Recovery
308 (18)	246 (14.4)	–	–	–	–	Recovery
340 (19.9)	219 (12.8)	77% of normal	Ultrasonogram: normal	–	15 days	Recovery
–	–	Normal	Ultrasonogram: hepatomegaly, hyperechogenicity favoring steatosis	–	<2 months	Recovery
508 (29.7)	155 (9.1)	85% of normal	Normal	–	<4 months	Recovery